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Vitamin D, Parathyroid Hormone, and Cardiovascular Events Among Older Adults

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Objectives The aim of this study was to evaluate associations of 25-hydroxyvitamin D (25-OHD) and parathyroid hormone (PTH) concentrations separately and in combination with incident cardiovascular events and mortality during 14 years of follow-up in the CHS (Cardiovascular Health Study).

Background Vitamin D deficiency and PTH excess are common in older adults and may adversely affect cardiovascular health.

Methods A total of 2,312 participants who were free of cardiovascular disease at baseline were studied. Vitamin D and intact PTH were measured from previously frozen serum using mass spectrometry and a 2-site immunoassay. Outcomes were adjudicated cases of myocardial infarction, heart failure, cardiovascular death, and all-cause mortality.

Results There were 384 participants (17%) with serum 25-OHD concentrations <15 ng/ml and 570 (25%) with serum PTH concentrations ≥65 pg/ml. After adjustment, each 10 ng/ml lower 25-OHD concentration was associated with a 9% greater (95% confidence interval [CI]: 2% to 17% greater) relative hazard of mortality and a 25% greater (95% CI: 8% to 44% greater) relative hazard of myocardial infarction. Serum 25-OHD concentrations <15 ng/ml were associated with a 29% greater (95% CI: 5% to 55% greater) risk for mortality. Serum PTH concentrations ≥65 pg/ml were associated with a 30% greater risk for heart failure (95% CI: 6% to 61% greater) but not other outcomes. There was no evidence of an interaction between serum 25-OHD and PTH concentrations and cardiovascular events.

Conclusions Among older adults, 25-OHD deficiency is associated with myocardial infarction and mortality; PTH excess is associated with heart failure. Vitamin D and PTH might influence cardiovascular risk through divergent pathways. (J Am Coll Cardiol 2011;58:1433–41) © 2011 by the American College of Cardiology Foundation

Disturbances in mineral metabolism are common in older adults and may adversely affect cardiovascular health (1,2). Older age is associated with lower circulating concentrations of 25-hydroxyvitamin D (25-OHD), impaired vitamin D activation within the kidney, and a rise in serum parathyroid hormone (PTH) concentrations (3,4). Disturbances in vitamin D and PTH metabolic axes may increase cardiovascular risk through diverse pathways (1,5,6). In experimental models, vitamin D deficiency activates the renin-angiotensin system, stimulates inflammatory cytokines, and promotes cardiomyocyte growth (7–9). PTH excess increases intracellular calcium in target tissues and is associated with hypertension, cardiac valve calcification, and left ventricular hypertrophy (10,11).

See page 1442

Previous studies of mineral metabolism and cardiovascular risk have generally focused on middle-aged populations and have evaluated 25-OHD and PTH concentrations separately. In the present study, we evaluated 25-OHD and PTH concentrations together in a general population of 2,312 ambulatory older adults who were free of clinical cardiovascular disease at baseline. We assessed associations

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JACC Vol. 58, No. 14, 2011
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Abbreviations and Acronyms

GFR = glomerular filtration rate

PTH = parathyroid hormone

25-OHD = 25-hydroxyvitamin D

of mineral metabolism biomarkers with adjudicated cases of incident myocardial infarction, incident heart failure, cardiovascular death, and all-cause mortality during 14 years of follow-up. We hypothesized that lower 25-OHD and higher PTH levels would be associated with cardiovascular events and that associations would be strongest in the presence of both disturbances, because PTH represents an endogenous biologic marker of inadequate vitamin D stores (12,13).

Methods

Study population. The CHS (Cardiovascular Health Study) is a prospective cohort study of clinical and subclinical cardiovascular disease among older patients (14). In 1989 and 1990, the CHS enrolled 5,201 ambulatory men and women age 65 years and older from Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. The CHS enrolled an additional 687 African American participants in 1992 and 1993. Exclusion criteria included the use of a wheelchair in the home, institutionalization, the need for a proxy respondent to provide informed consent, plans to move from the area within 3 years, and current treatment for cancer. Each center's institutional review board approved the study, and all participants provided informed consent.

We evaluated CHS participants at the time of their 1992 and 1993 examinations. To focus on incident cardiovascular events, we excluded participants who had prevalent cardiovascular disease at the time of the 1992 and 1993 CHS exams, defined as any 1 of the following conditions: coronary heart disease, heart failure, stroke, transient ischemic attack, claudication, atrial fibrillation, pacemaker, or implantable cardioverter-defibrillator (Fig. 1). CHS investigators determined prevalent cardiovascular conditions by review of medical records, electrocardiographic findings, participant responses to questionnaires, and interim events that occurred between the baseline and 1992 and 1993 CHS

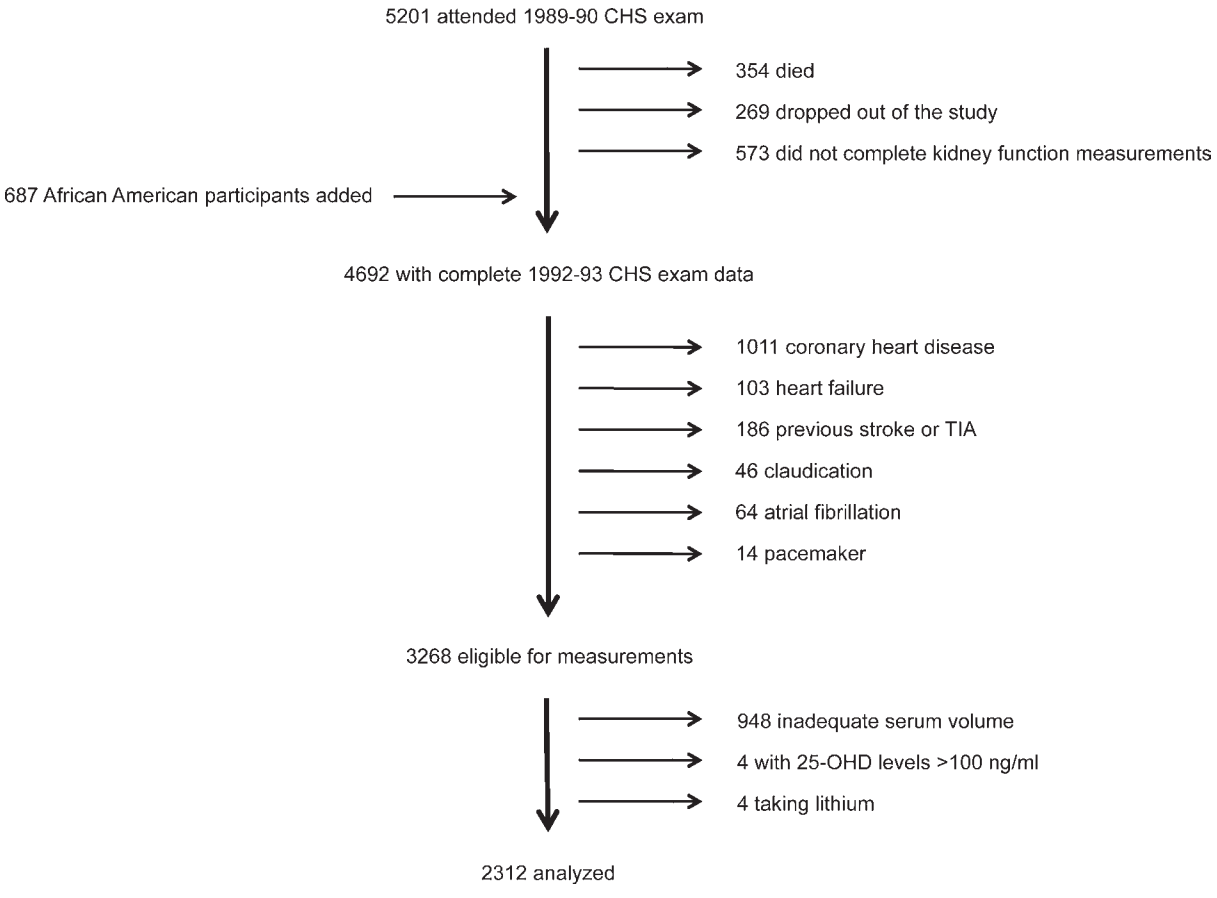

Figure 1 Flow Diagram of the Study Population

Exclusions are shown on the **right side** of the figure; additions to the study population are shown on the **left**.
CHS = Cardiovascular Health Study; TIA = transient ischemic attack; 25-OHD = 25-hydroxyvitamin D.

examinations (15). We further excluded 948 participants who had inadequate serum volumes (<500 μl) to perform the mineral metabolism measurements, 4 participants who had implausible 25-OHD concentrations (>100 ng/ml), and 4 participants who were taking lithium, which may alter calcium metabolism, resulting in a final study sample of 2,312 participants. Compared with participants excluded because of inadequate sample volumes, included subjects were older (73.9 years vs. 71.9 years) and more likely to be Caucasian (85% vs. 75%).

Measurement of mineral metabolism variables. The Laboratory for Clinical Biochemistry Research at the University of Vermont stored serum samples at −70°C using established methods, which have demonstrated long-term stability for serum markers of coagulation, fibrinolysis, and inflammation (16). The University of Washington Clinical Nutrition Research Unit performed mineral metabolism measurements from serum collected during the 1992 and 1993 CHS exams. Total 25-OHD (25-OHD_2 + 25-OHD_3) was measured using high-performance liquid chromatography and tandem mass spectrometry on a Waters Quattro micro mass spectrometer (Waters, Milford, Massachusetts). The interassay coefficient of variation was <3.4%. Intact serum PTH was quantified using a 2-site immunoassay on a Beckman UniCel DxI clinical analyzer (Beckman Coulter, Brea, California). The reference range is 17 to 66 pg/ml, as determined from the central 95% of values from 43 normal laboratory personnel with normal 25-OHD concentrations in March 2005. The interassay coefficient of variation for PTH was <4.5% at 37 pg/ml. Serum nonionized total calcium levels were measured using indirect potentiometry, and serum phosphorus levels were measured using a timed-rate colorimetric reaction method with ammonium molybdate on a Beckman DxC Synchron analyzer (Beckman Coulter).

Ascertainment of cardiovascular outcomes. Study outcomes were all-cause mortality, cardiovascular mortality, incident heart failure, and incident myocardial infarction. CHS investigators identified potential cardiovascular events semiannually via telephone surveillance and annually by repeat interviews and examinations. The CHS events committee adjudicated cardiovascular events using available hospital discharge summaries, diagnostic test reports, surgical and radiologic findings, consultation reports, autopsies, and death certificates (17). The committee defined heart failure by a physician diagnosis of heart failure plus documentation of symptoms and signs of heart failure, pulmonary edema on chest x-ray, or specific medical treatment for heart failure. Echocardiographic results, when available, were also considered during adjudication. The committee defined acute myocardial infarction using an algorithm that included elements of chest pain, cardiac enzymes, and electrocardiographic changes. The committee defined cardiovascular mortality as death due to acute myocardial infarction, atherosclerotic coronary heart disease, ischemic or hemorrhagic stroke, or other cardiovascular cause (ruptured aortic aneurysm, peripheral vascular disease, valvular heart disease, or pulmonary embolism). Cardiovascular event data were complete through June 30, 2007. Because participant data are linked with Medicare records and the National Death Index, follow-up is considered to be 100% complete for each of the study outcomes evaluated here.

Measurement of other study variables. Trained CHS study personnel conducted standardized interviews, which queried demographics, health status, smoking status, and alcohol use (14). Study participants were asked about the frequency and duration of 15 common leisure-time activities during the previous 2 weeks, and CHS investigators calculated a total weighted leisure time physical activity score on the basis of these responses. CHS study personnel assessed prescription and over-the-counter medication use, including vitamin D supplements, by instructing participants to bring in all of their medications and directly transcribing the medication bottle labels. We queried medication lists to identify vitamin D and calcium supplement use. CHS study personnel measured blood pressure in triplicate 5 min apart with the participant seated and performed phlebotomy under fasting conditions.

CHS investigators defined diabetes as a fasting glucose level >7.0 mmol/l or the use of insulin or an oral hypoglycemic medication. We calculated body mass index as height/$(\text{weight})^2$, where height and weight were measured in meters and kilograms, respectively. We analyzed education level as none through grade 9, high school, and professional or vocational. The Laboratory for Clinical Biochemistry Research analyzed blood specimens for albumin, total and high-density lipoprotein cholesterol, creatinine, and C-reactive protein. Low-density lipoprotein cholesterol was calculated using the Friedewald equation. CHS investigators measured cystatin C levels from previously collected serum samples stored at −70°C using a particle-enhanced immunonephelometric assay with a nephelometer (BNII, Siemens Healthcare Diagnostics, Inc, Deerfield, Illinois) (18). We calculated estimated glomerular filtration rate (GFR) as estimated $\text{GFR}_{\text{cystatin C}} = 76.7 \times (\text{cystatin C})^{-1.19}$. This equation, derived in a recent pooling study of 3,418 adults who underwent simultaneous cystatin C measurements and gold-standard radionucleotide measurements of GFR, explains approximately 82% of the variation in directly measured GFR in the setting of chronic kidney disease (19).

Statistical analysis. We analyzed 25-OHD as a continuous variable because functional analyses revealed linear associations of serum 25-OHD concentrations with study outcomes. We also evaluated 25-OHD according to previously published categories (20–22). We analyzed serum PTH concentrations as <65 pg/ml versus ≥65 pg/ml, because functional analyses revealed threshold associations of serum PTH concentration ≥65 pg/ml with each of the study outcomes and because 65 pg/ml represents the upper limit of normal for this assay on the basis of the central 95% of values from healthy subjects who had normal 25-OHD

concentrations. We defined primary hyperparathyroidism as a serum PTH concentration ≥65 pg/ml plus a serum calcium concentration >10.2 mg/dl, as previously published (23). We used Spearman's correlation to describe univariate associations between serum 25-OHD and PTH concentrations.

We defined time at risk as the elapsed time from the 1992 and 1993 examinations until the first occurrence of each outcome of interest. We censored analyses of nonfatal outcomes for mortality and censored analyses of cardiovascular mortality for noncardiovascular death. We constructed nested Cox proportional hazards models to estimate the relative hazard of each study outcome after adjustment for relevant confounding variables (24). A basic model included 25-OHD and PTH levels and adjusted for age, race, sex, season of the year, and clinic site. A second model added cardiovascular risk factors (diabetes, antihypertensive medications, smoking, education, physical activity, body mass index, systolic blood pressure, C-reactive protein, and total and high-density lipoprotein cholesterol), and serum concentrations of calcium and phosphorus. A third model added GFR, estimated by serum cystatin C concentrations, to separately describe the confounding influence of kidney function. We analyzed kilocalories of physical activity, body mass index, systolic blood pressure, and levels of CRP, lipids, calcium, phosphorus, and estimated GFR as continuous variables in the multivariate models. We assessed the functional associations of 25-OHD and PTH concentrations with study outcomes by constructing spline models after basic adjustment for covariates specified in model 1. The proportional hazards assumption was satisfied for all models ($p > 0.20$), indicating statistically similar relative risks of each study outcome over time.

We looked for evidence of an interaction between 25-OHD deficiency and PTH excess by calculating the relative excess risk of interaction. A relative excess risk of interaction of 0 indicates no additive biological interaction. We performed stratified analyses to explore whether associations of 25-OHD with study outcomes might differ according to baseline characteristics. We conducted analyses using S-Plus version 8.0 (Tibco, Seattle, Washington) and SPSS version 15.0.1.1 (SPSS Inc., Chicago, Illinois).

Results

Description of vitamin D and PTH concentrations. Serum 25-OHD concentrations were normally distributed, with a mean value of 25.2 ± 10.2 ng/ml (interquartile range: 17.8 to 31.5 ng/ml). The prevalences of vitamin D deficiency (<15 ng/ml) and insufficiency (15 to 30 ng/ml) were 16.6% and 53.9%, respectively. Serum 25-OHD concentrations were highest among participants from the Sacramento site (mean 26.4 ± 10.5 ng/ml) and lowest among participants from the Pittsburgh site (mean 24.4 ± 11.5 ng/ml). The distribution of serum PTH concentrations was right skewed, with a median value of 51 pg/ml (SD 29.7 pg/ml; interquartile range: 39 to 65 pg/ml). Serum 25-OHD concentrations were inversely correlated with serum PTH concentrations (correlation coefficient = −0.317).

Associations of vitamin D and PTH with baseline characteristics. Lower serum 25-OHD concentrations were related to African American race, female sex, measurement during winter months, prevalent diabetes, current smoking, greater body mass index, lesser physical activity, higher systolic blood pressure, and higher serum CRP concentrations (Table 1). The prevalence of vitamin D deficiency was more than 3-fold greater among African Americans compared with Caucasians (42.9% vs. 12.2%). Serum 25-OHD concentrations were not associated with estimated GFR. Higher serum PTH concentrations were associated with African American race, female sex, higher systolic blood pressure, and lower estimated GFR. Serum calcium and phosphorus concentrations did not vary across categories of 25-OHD, although serum phosphorus concentrations were slightly lower among participants who had serum PTH concentrations ≥65 pg/ml.

Associations of 25-OHD with study outcomes. During a median follow-up period of 14.0 years (interquartile range: 8.5 to 14.6 years), there were 1,226 deaths, of which 389 (32%) were classified as cardiovascular, 504 incident cases of heart failure, and 299 incident myocardial infarctions. In a minimally adjusted model that included serum PTH concentration, age, race, sex, season, and clinic site, each 10 ng/ml lower serum 25-OHD concentration was associated with all-cause mortality and incident myocardial infarction but not with cardiovascular death or incident heart failure (Table 2). Further adjustment for traditional cardiovascular risk factors plus serum calcium and phosphorus modestly attenuated associations of 25-OHD with mortality and myocardial infarction; adjustment for estimated kidney function did not appreciably alter these associations. After full adjustment, each 10 ng/ml lower 25-OHD concentration was associated with a 9% greater relative risk for all-cause mortality (95% confidence interval: 2% to 17% greater; $p = 0.012$) and a 25% greater relative risk for incident myocardial infarction (95% confidence interval: 8% to 44% greater; $p = 0.002$). These associations were not appreciably altered by additional adjustment for calcium and vitamin D supplementation. Neither serum calcium nor serum phosphorus concentrations were associated with any of the cardiovascular outcomes in this study population.

To further address the possibility of confounding and to explore potential interactions, we estimated associations of lower 25-OHD concentrations with mortality and myocardial infarction across categories of physical activity level, body mass index, age, race, sex, and estimated kidney function (Fig. 2). Associations were generally similar, with widely overlapping confidence intervals.

Associations of PTH with study outcomes. After basic adjustment, serum PTH concentrations ≥65 pg/ml were associated with cardiovascular death and incident heart failure but not with all-cause mortality or myocardial in-

Table 1 Baseline Characteristics by PTH and 25-OHD Concentrations

Variable	25-OHD (ng/ml)			PTH (pg/ml)	
	>30	15–30	<15	<65	≥65
Number of participants	681 (29%)	1,247 (54%)	384 (17%)	1,742 (75%)	570 (25%)
Demographic data					
Age (yrs)	73 ± 4	74 ± 5	74 ± 6	74 ± 5	75 ± 6
African Americans	30 (4%)	160 (13%)	142 (37%)	226 (13%)	107 (19%)
Men	287 (42%)	335 (27%)	79 (21%)	555 (32%)	146 (26%)
Season					
Winter	112 (16%)	303 (24%)	169 (44%)	413 (24%)	171 (30%)
Spring	109 (16%)	302 (24%)	118 (31%)	386 (22%)	143 (25%)
Summer	286 (42%)	339 (27%)	45 (12%)	538 (31%)	132 (23%)
Autumn	174 (26%)	303 (24%)	52 (14%)	405 (23%)	124 (22%)
Site					
Forsyth County, North Carolina	195 (29%)	387 (31%)	103 (27%)	513 (30%)	172 (30%)
Sacramento County, California	199 (29%)	264 (21%)	94 (24%)	390 (22%)	167 (29%)
Washington County, Maryland	152 (22%)	334 (27%)	76 (20%)	449 (26%)	113 (20%)
Pittsburgh, Pennsylvania	135 (20%)	262 (21%)	111 (29%)	390 (22%)	118 (21%)
Diabetes	55 (8%)	134 (11%)	76 (20%)	196 (11%)	69 (12%)
Medication use					
Any antihypertensive agent	252 (37%)	486 (39%)	187 (49%)	663 (38%)	262 (46%)
Thiazide diuretic agent	56 (8%)	131 (11%)	53 (14%)	183 (11%)	57 (10%)
Loop diuretic agent	15 (2%)	45 (4%)	16 (4%)	39 (2%)	37 (7%)
Vitamin D supplement	10 (1.5%)	0 (0%)	0 (0%)	8 (0.5%)	2 (0.4%)
Calcium supplement	7 (1.0%)	9 (0.7%)	2 (0.5%)	16 (0.9%)	2 (0.4%)
Current smoking	54 (8%)	116 (10%)	58 (16%)	180 (10%)	48 (9%)
Education level					
None through grade 9	73 (11%)	207 (17%)	87 (23%)	262 (15%)	105 (18%)
High school	256 (38%)	469 (38%)	145 (38%)	654 (38%)	216 (38%)
Professional/vocational	349 (51%)	569 (46%)	151 (39%)	823 (47%)	246 (43%)
Physical activity (kcal/week)	2,479 ± 2,421	1,772 ± 1,911	1,243 ± 1,676	1,964 ± 2,111	1,672 ± 1,978
Physical examination data					
Body mass index (kg/m^2)	25.5 ± 3.9	27.1 ± 4.8	27.9 ± 5.5	26.4 ± 4.5	27.8 ± 5.4
Systolic blood pressure (mm Hg)	134 ± 20	136 ± 21	140 ± 21	135 ± 20	142 ± 23
Serum measurements					
PTH (pg/ml)	49 ± 27	57 ± 26	71 ± 39	44 ± 12	94 ± 37
25-OHD (ng/ml)	37 ± 8	23 ± 4	11 ± 3	27 ± 10	21 ± 9
Calcium (mg/dl)	9.5 ± 0.3	9.5 ± 0.4	9.5 ± 0.4	9.5 ± 0.4	9.5 ± 0.4
Phosphorus (mg/dl)	3.6 ± 0.5	3.6 ± 0.5	3.6 ± 0.5	3.6 ± 0.5	3.5 ± 0.5
Estimated GFR$_{cystatin\ C}$ (ml/min/1.73 m^2)	75 ± 18	76 ± 18	76 ± 19	77 ± 17	72 ± 20
CRP (mg/l)	4.3 ± 8.5	4.7 ± 7.9	6.1 ± 9.2	4.7 ± 8.6	5.0 ± 7.5
Total cholesterol (mg/dl)	210 ± 37	211 ± 35	212 ± 39	210 ± 36	214 ± 39
High-density lipoprotein (mg/dl)	57 ± 16	55 ± 14	56 ± 14	56 ± 15	54 ± 14

Values are n (%) or mean ± SD.
CRP = C-reactive protein; GFR = glomerular filtration rate; PTH = parathyroid hormone; 25-OHD = 25-hydroxyvitamin D.

farction (Table 3, model 1). Associations of PTH excess with cardiovascular outcomes were confounded by kidney function; adjustment for estimated GFR removed the statistical association with cardiovascular death and attenuated the association with heart failure (Table 3, model 3). After full adjustment, PTH concentrations ≥65 pg/ml remained associated with an estimated 30% greater risk for heart failure (95% confidence interval: 6% to 61% greater). This association was not altered by excluding 21 subjects who met the definition of primary hyperparathyroidism (adjusted hazard ratio: 1.29; 95% confidence interval: 1.04 to 1.59) or by additional adjustment for thiazide diuretic use (adjusted hazard ratio: 1.29; 95% confidence interval: 1.04 to 1.61). When analyzed as a continuous variable, serum PTH was not associated with any of the study outcomes.

Combined associations of 25-OHD and PTH with study outcomes. The combination of vitamin D deficiency and PTH excess tended to be associated with greater risks of cardiovascular outcomes, but these differences were not statistically significant (Table 4). We further looked for evidence of additive interactions between serum 25-OHD and PTH concentrations and cardiovascular events. The relative excess risk of interaction was not statistically significant for any of the 4 cardiovascular outcomes (all $p > 0.30$).

JACC Vol. 58, No. 14, 2011
September 27, 2011:1433–41

Table 2 Associations of Serum 25-OHD Concentration With Study Outcomes

Variable	Number	Events	Model 1*	Model 2†	Model 3‡
All-cause mortality	2,312	1,226			
25-OHD >30 ng/ml	681	329	1.00	1.00	1.00
25-OHD 15–30 ng/ml	1,247	668	1.14 (0.99–1.31)	1.10 (0.95–1.27)	1.15 (1.00–1.33)
25-OHD <15 ng/ml	384	229	1.36 (1.12–1.66)	1.21 (0.99–1.48)	1.29 (1.05–1.57)
Continuous per 10 ng/ml lower 25-OHD			1.10 (1.03–1.17)	1.05 (0.99–1.13)	1.09 (1.02–1.17)
p value (continuous)			0.005	0.122	0.012
Cardiovascular mortality	2,312	389			
25-OHD >30 ng/ml	681	107	1.00	1.00	1.00
25-OHD 15–30 ng/ml	1,247	207	1.00 (0.78–1.29)	0.95 (0.74–1.23)	1.01 (0.78–1.30)
25-OHD <15 ng/ml	384	75	1.24 (0.88–1.76)	1.08 (0.76–1.54)	1.17 (0.83–1.67)
Continuous per 10 ng/ml lower 25-OHD			1.07 (0.95–1.20)	1.02 (0.90–1.14)	1.06 (0.94–1.19)
p value (continuous)			0.247	0.795	0.356
Incident heart failure	2,312	504			
25-OHD >30 ng/ml	681	107	1.00	1.00	1.00
25-OHD 15–30 ng/ml	1,247	207	1.00 (0.78–1.29)	0.95 (0.74–1.23)	1.01 (0.78–1.30)
25-OHD <15 ng/ml	384	75	1.24 (0.88–1.76)	1.08 (0.76–1.54)	1.17 (0.83–1.67)
Continuous per 10 ng/ml lower 25-OHD			0.99 (0.90–1.09)	0.92 (0.83–1.02)	0.95 (0.86–1.05)
p value (continuous)			0.861	0.100	0.303
Incident myocardial infarction	2,312	299			
25-OHD >30 ng/ml	681	88	1.00	1.00	1.00
25-OHD 15–30 ng/ml	1,247	161	1.17 (0.89–1.54)	1.17 (0.88–1.55)	1.20 (0.90–1.59)
25-OHD <15 ng/ml	384	50	1.41 (0.94–2.11)	1.37 (0.90–2.07)	1.40 (0.93–2.12)
Continuous per 10 ng/ml lower 25-OHD			1.25 (1.09–1.43)	1.23 (1.07–1.42)	1.25 (1.08–1.44)
p value (continuous)			0.001	0.004	0.002

Values are n or adjusted hazard ratio (95% confidence interval). *Model 1 includes 25-OHD and parathyroid hormone levels and is adjusted for age, race, sex, season of the year, and clinic site. †Model 2 adds diabetes, antihypertensive medications, smoking (never, current, former), education, kilocalories of physical activity, body mass index, systolic blood pressure, levels of C-reactive protein, total, high-density lipoprotein cholesterol, calcium, and phosphorus. ‡Model 3 adds estimated glomerular filtration rate$_{\text{cystatin C}}$.
25-OHD = 25-hydroxyvitamin D.

Discussion

In this community-based cohort of ambulatory older adults without clinical cardiovascular disease, lower serum 25-OHD concentrations were associated with all-cause mortality and incident myocardial infarction, whereas higher serum PTH concentrations were associated with incident heart failure. We did not detect an interaction of 25-OHD and PTH on cardiovascular outcomes in this study population. This study has several important strengths, which include a generally healthy study population that was free of clinical cardiovascular disease at baseline, more than twice the length of follow-up compared with previous studies, a large number of adjudicated cardiovascular events and cardiovascular causes of death, and the use of standardized methods to assess mineral metabolism markers, cardiovascular risk factors, kidney function, and comorbid conditions.

In middle-aged populations, lower 25-OHD concentrations are associated with incident myocardial infarction and all-cause mortality (20,25,26). Associations of lower 25-OHD concentrations with cardiovascular death, defined using administrative codes, have recently been reported in older populations from the U.S. and Europe (27,28). However, diagnosis codes and/or death certificate data are known to misclassify cardiovascular events and causes of death in older people (29,30).

We found higher serum PTH levels to be associated with an estimated 18% greater risk for cardiovascular death, but this result was not statistically significant (95% confidence interval: 0.92 to 1.50). In contrast, Hagström et al. (31) reported a statistically significant association of higher PTH concentrations with cardiovascular death among older Swedish men. The relatively healthy makeup of our study populations and more specific definition of cardiovascular death in the CHS may have reduced study power to detect associations with this outcome.

Lower serum 25-OHD concentrations represent decreased vitamin D stores, whereas serum PTH excess reflects, in part, inadequate biologic vitamin D activity (5,32,33). On the basis of these relationships, we hypothesized that associations of lower 25-OHD concentrations with cardiovascular outcomes would be strongest in the presence of concomitant PTH excess. However, our findings do not support such an interaction. Moreover, 25-OHD and PTH concentrations tended to be associated with different cardiovascular outcomes in this study. These findings are more compatible with the hypothesis that 25-OHD and PTH might influence cardiovascular risk through divergent pathways.

The biologic actions of 25-OHD and PTH may explain their associations with myocardial infarction and heart failure. In previous studies, lower 25-OHD concentrations were associated with metabolic risk factors for atheroscle-

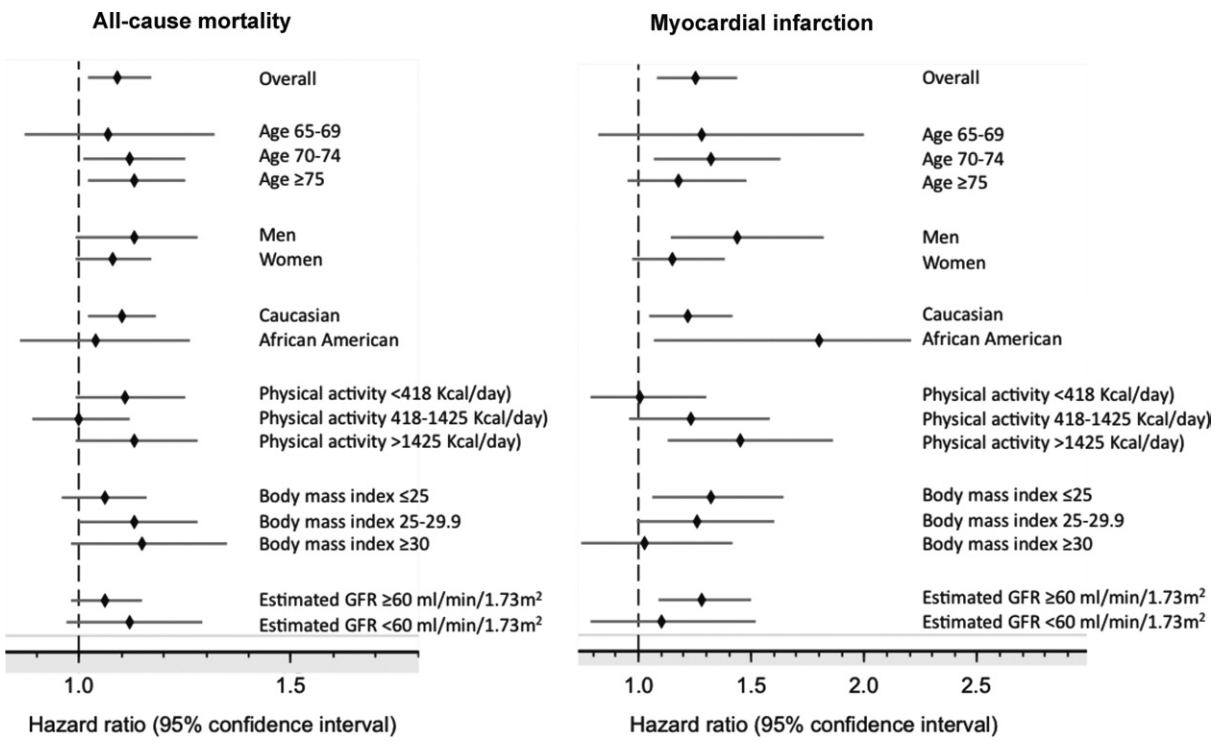

Figure 2 **Association of 25-OHD Concentration With Mortality and Myocardial Infarction by Subgroups**

Continuous associations of 10 ng/ml lower 25-hydroxyvitamin D (25-OHD) concentration with all-cause mortality and incident myocardial infarction by subgroups, adjusted for the covariates in model 3. GFR = glomerular filtration rate.

rosis, including diabetes, hypertension, and inflammation (34–36). Cell culture studies and in vivo animal models have demonstrated immunomodulatory actions of vitamin D (8,37), and vitamin D increases insulin receptor expression and insulin responsiveness for glucose transport in cultured human promonocytic cells (38). Hyperparathyroid-

Table 3 **Associations of Serum PTH Concentration With Study Outcomes**

			Adjusted Hazard Ratio (95% Confidence Interval)		
Variable	Number	Events	Model 1*	Model 2†	Model 3‡
All-cause mortality					
PTH <65 pg/ml	1,742	899	1.00	1.00	1.00
PTH ≥65 pg/ml	570	327	1.11 (0.97–1.28)	1.14 (0.99–1.31)	1.07 (0.93–1.23)
p value			0.125	0.035	0.341
Cardiovascular mortality					
PTH <65 pg/ml	1,742	273	1.00	1.00	1.00
PTH ≥65 pg/ml	570	116	1.30 (1.03–1.65)	1.30 (1.01–1.66)	1.16 (0.90–1.50)
p value			0.030	0.040	0.213
Incident heart failure					
PTH <65 pg/ml	1,742	351	1.00	1.00	1.00
PTH ≥65 pg/ml	570	153	1.47 (1.19–1.80)	1.40 (1.13–1.73)	1.30 (1.05–1.61)
p value			<0.001	0.003	0.018
Incident myocardial infarction					
PTH <65 pg/ml	1,742	223	1.00	1.00	1.00
PTH ≥65 pg/ml	570	76	1.05 (0.79–1.40)	1.01 (0.76–1.35)	0.98 (0.74–1.31)
p value			0.719	0.994	0.793

*Model 1 includes 25-hydroxyvitamin D and PTH levels and is adjusted for age, race, sex, season of the year, and clinic site. †Model 2 adds diabetes, antihypertensive medications, smoking (never, current, former), education, kilocalories of physical activity, body mass index, systolic blood pressure, levels of C-reactive protein, total, high-density lipoprotein cholesterol, calcium, and phosphorus. ‡Model 3 adds estimated glomerular filtration rate$_{cystatin\ C}$.
PTH = parathyroid hormone.

JACC Vol. 58, No. 14, 2011
September 27, 2011:1433–41

Table 4 Combined Associations of 25-OHD and PTH Concentrations With Study Outcomes

Variable	Adjusted Hazard Ratio (95% Confidence Interval)		p Value for Interaction
	PTH <65 pg/ml	PTH ≥65 pg/ml	
All-cause mortality			
25-OHD >30 ng/ml	1.00	1.15 (0.82–1.60)	
25-OHD 15–30 ng/ml	1.18 (1.01–1.37)	1.21 (0.98–1.49)	
25-OHD <15 ng/ml	1.27 (1.00–1.61)	1.43 (1.11–1.85)	0.775
Cardiovascular mortality			
25-OHD >30 ng/ml	1.00	0.97 (0.54–1.76)	
25-OHD 15–30 ng/ml	0.96 (0.73–1.27)	1.20 (0.85–1.71)	
25-OHD <15 ng/ml	1.15 (0.76–1.74)	1.32 (0.83–2.08)	0.745
Heart failure			
25-OHD >30 ng/ml	1.00	1.35 (0.85–2.15)	
25-OHD 15–30 ng/ml	1.03 (0.81–1.32)	1.39 (1.02–1.88)	
25-OHD <15 ng/ml	0.85 (0.57–1.26)	0.95 (0.61–1.46)	0.774
Myocardial infarction			
25-OHD >30 ng/ml	1.00	1.09 (0.58–2.02)	
25-OHD 15–30 ng/ml	1.25 (0.92–1.70)	1.05 (0.68–1.62)	
25-OHD <15 ng/ml	1.30 (0.79–2.13)	1.55 (0.91–2.62)	0.562

Hazard ratios adjusted for age, race, sex, season of the year, clinic site, diabetes, antihypertensive medications, smoking (never, current, former), education, kilocalories of physical activity, body mass index, systolic blood pressure, serum levels of C-reactive protein, total and high-density lipoprotein cholesterol, calcium, phosphorus, and estimated glomerular filtration rate$_{\text{cystatin C}}$.
PTH = parathyroid hormone; 25-OHD = 25-hydroxyvitamin D.

ism, a state of chronic PTH excess, has been linked with arterial stiffness and hypertension. The prevalence of hypertension among patients with primary hyperparathyroidism ranges from 30% to 70%, and blood pressure decreases after surgical parathyroidectomy (39–41). PTH exerts a trophic effect on cardiomyocytes, with an increase in total cellular mass, and higher serum PTH concentrations are associated with left ventricular hypertrophy in the general population (11,42).

Study limitations. These observational data cannot prove that 25-OHD deficiency or PTH excess plays a causal role in the development of cardiovascular disease. These serologic markers may be indicators of health status, in particular 25-OHD deficiency, which may reflect comorbidity, less time spent outdoors, and inadequate nutrient intake. We attempted to address potential confounding in this study by excluding individuals with pre-existing cardiovascular diseases and by adjusting for lifestyle factors, comorbidity, and cardiovascular risk factors that were measured using uniform methods. Adjusted models included some factors that could reside on the hypothesized causal pathway between mineral metabolism disturbances and cardiovascular events, such as hypertension, diabetes, and inflammation. Adjustment for estimated GFR using cystatin C levels was particularly important for appreciating the confounding influence of kidney function on the associations of PTH with cardiovascular mortality. A rise in serum PTH is 1 of the first detectable mineral metabolism disturbances of chronic kidney disease (43), which is highly prevalent in older adults and may be difficult to detect using traditional serologic markers.

A second limitation of this study was the use of a single measurement of 25-OHD and PTH later in life. Biologic variation in these markers within an individual over time is expected. The prospective design of this study favors nondifferential misclassification of 25-OHD and PTH concentrations, which would be expected to dilute the observed associations. Future studies of mineral metabolism markers and cardiovascular disease outcomes would benefit from multiple measurements within a subject over time. The CHS focused exclusively on older adults; associations of mineral metabolism markers with cardiovascular events may differ in younger and more ethnically diverse populations.

Conclusions

Consistent associations of 25-OHD concentrations with cardiovascular outcomes across multiple cohort studies and compelling biologic evidence for a beneficial effect of vitamin D on cardiovascular health support clinical trials of vitamin D therapy as the next step to test whether observed associations are truly causal. Associations of PTH excess with cardiovascular diseases are emerging and motivate further epidemiological work in diverse populations to better understand functional relationships and to determine specific populations in which associations may be strongest.

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Key Words: cardiovascular death ■ heart failure ■ mineral metabolism ■ myocardial infarction ■ parathyroid hormone ■ vitamin D.